PATENT
Docket No. 312762001530

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Tami M. Procopio

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Ann MONOSOV and Xinyu Fu.

Serial No.: 09/023,232

Filing Date: 13 February 1998

For: NUDE MOUSE MODEL FOR HUMAN NEOPLASTIC DISEASE

Examiner: Ann Marie S. Beckerleg

Group Art Unit: 1632

DECLARATION OF ROBERT M. HOFFMAN

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, ROBERT M. HOFFMAN, declare as follows:

1. I am a Professor in the Department of Surgery at the University of California San Diego Medical Center and am Chairman of the Board and Chief Executive Officer of AntiCancer, Inc., the assignee herein. I obtained my Ph.D. in biology from Harvard University in 1971 and have been practicing in the field of cancer research since that time. I have held academic positions at Harvard Medical School and at the Weizmann Institute and have published numerous articles on subjects related to cancer and metastasis. I am on the editorial boards of *AntiCancer Research* and of *In Vitro Cellular and Developmental Biology*. A copy of my *curriculum vitae* is attached hereto as Exhibit 1.

2. I have supervised research at AntiCancer, Inc., which employs the surgical orthotopic implantation of intact tumor tissue as claimed in the herein application. The research has resulted in the publication of numerous papers establishing that the model successfully mimics, in an immunocompromised rodent, the clinical course of tumor growth and metastasis. The results using this model are dramatically superior to those obtained by Kyriazis, Otto, Wang or McLemore.

3. The clinical course of various tumors is described in the standard reference work of Holland, James E., *et al.*, editor, Cancer Medicine, 5th ed., B.C. Decker, Inc., Hamilton, Ontario, Canada (2000). This document is referred to as citation No. 2 in Exhibit 2 attached hereto and as citation No. 3 in Exhibit 3.

4. Exhibit 2 summarizes the results obtained using the methods of Kyriazis as compared to the model claimed in the present application, designated "AntiCancer Metamouse." The numbers in parentheses refer to the documents cited on pages 5 and 6 of Exhibit 2. All of these documents, with the exception of Nos. 2 and 19 are the results of experiments which I supervised.

5. Page 1 of Exhibit 2 shows a comparison of results using various bladder cancers. As shown in the chart on that page, the clinical pattern of metastasis as established by Holland, *et al.*, is successfully mimicked by the AntiCancer MetaMouse model, but incomplete or negative results were obtained by Kyriazis.

6. Similar comparisons are shown on pages 2-4 of Exhibit 1 for colon cancer, pancreatic cancer and breast cancer. In every case, only limited metastases were shown using the method of Kyriazis as reported in the Kyriazis paper cited by the Office, while the

AntiCancer model clearly showed extensive metastases in accordance with the clinical progress of the disease in every case.

7. Exhibit 3 compares the results obtained by Otto with those using the AntiCancer model. While Otto failed to obtain metastases with renal cell carcinoma, the AntiCancer model showed metastases, as would be found in clinical disease, into the lung, lymph nodes and liver.

8. We have also used the techniques described and claimed in the above-referenced application to study the metastasis of lung cancer. Extensive metastasis is consistently obtained as described in Yang, M, *et al., Cancer Res.* (1998) 58:5217-5221 and by Rashidi, B., *et al., Clin. Exp. Metas.* (2000) 18:57-60. These papers are attached as Exhibits 4 and 5.

9. I also attach a summary that I prepared in 1999 as to the efficacy of the model described in the present application. This was published in *Investigational New Drugs* (1999) 17:343-359 and is attached as Exhibit 6. This paper reviews the history over the last 10 or so years of this very useful model.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Executed at San Diego, California, on 13 May 2002.

ROBERT M. HOFFMAN